



FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO



Fondazione D'Amico
per la Ricerca
sulle Malattie Renali



28° Congresso Nazionale

della SOCIETÀ ITALIANA di NEFROLOGIA PEDIATRICA

24-26 Ottobre 2012

Milano, 26/10/2012

Le recenti scoperte sulla comunicazione tra i podociti aprono nuove prospettive diagnostiche e terapeutiche per la Sindrome Nefrosica?

MP Rastaldi

Renal Research Laboratory

Fondazione IRCCS Policlinico & Fondazione D'Amico

Milan, Italy

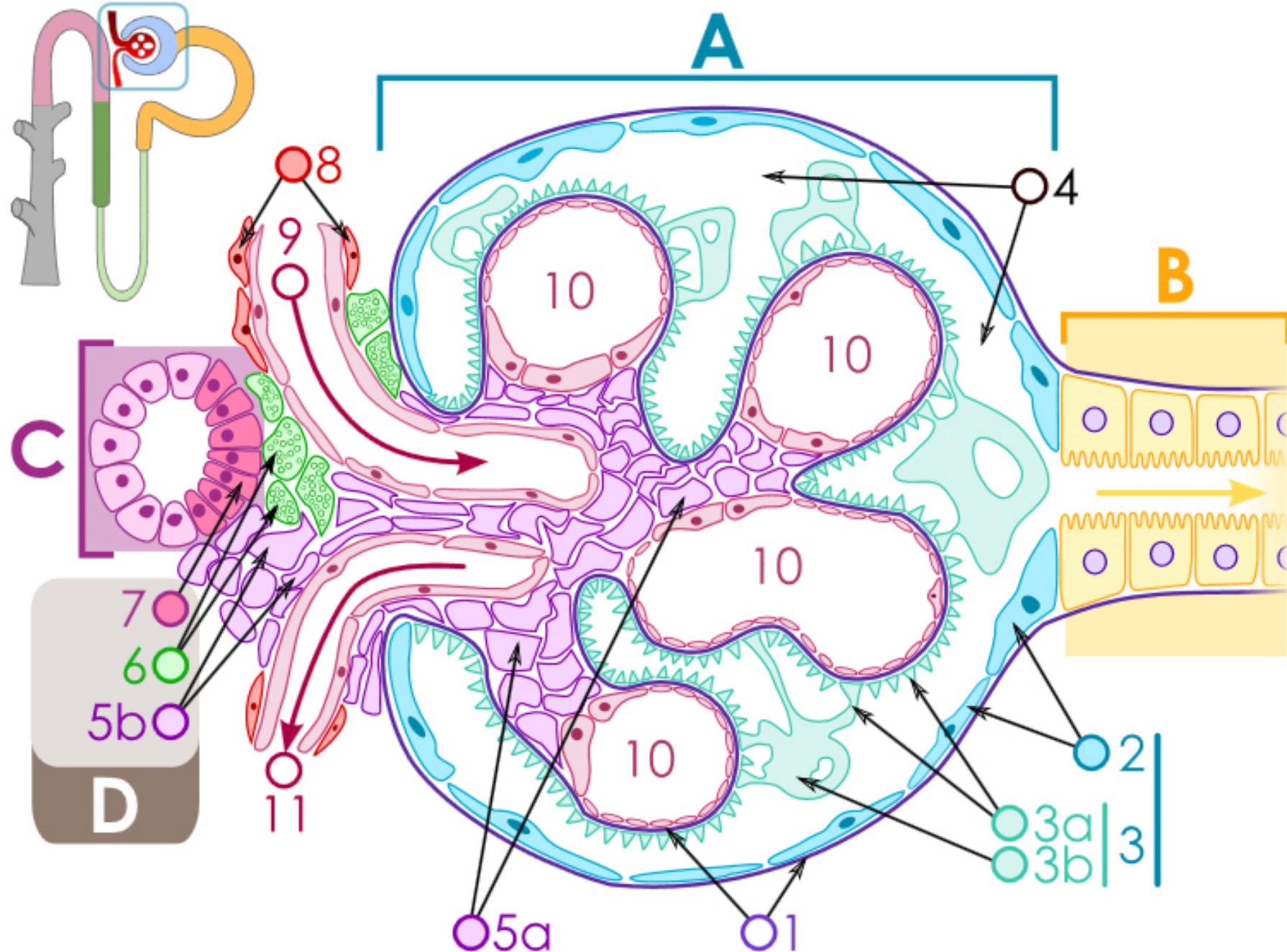


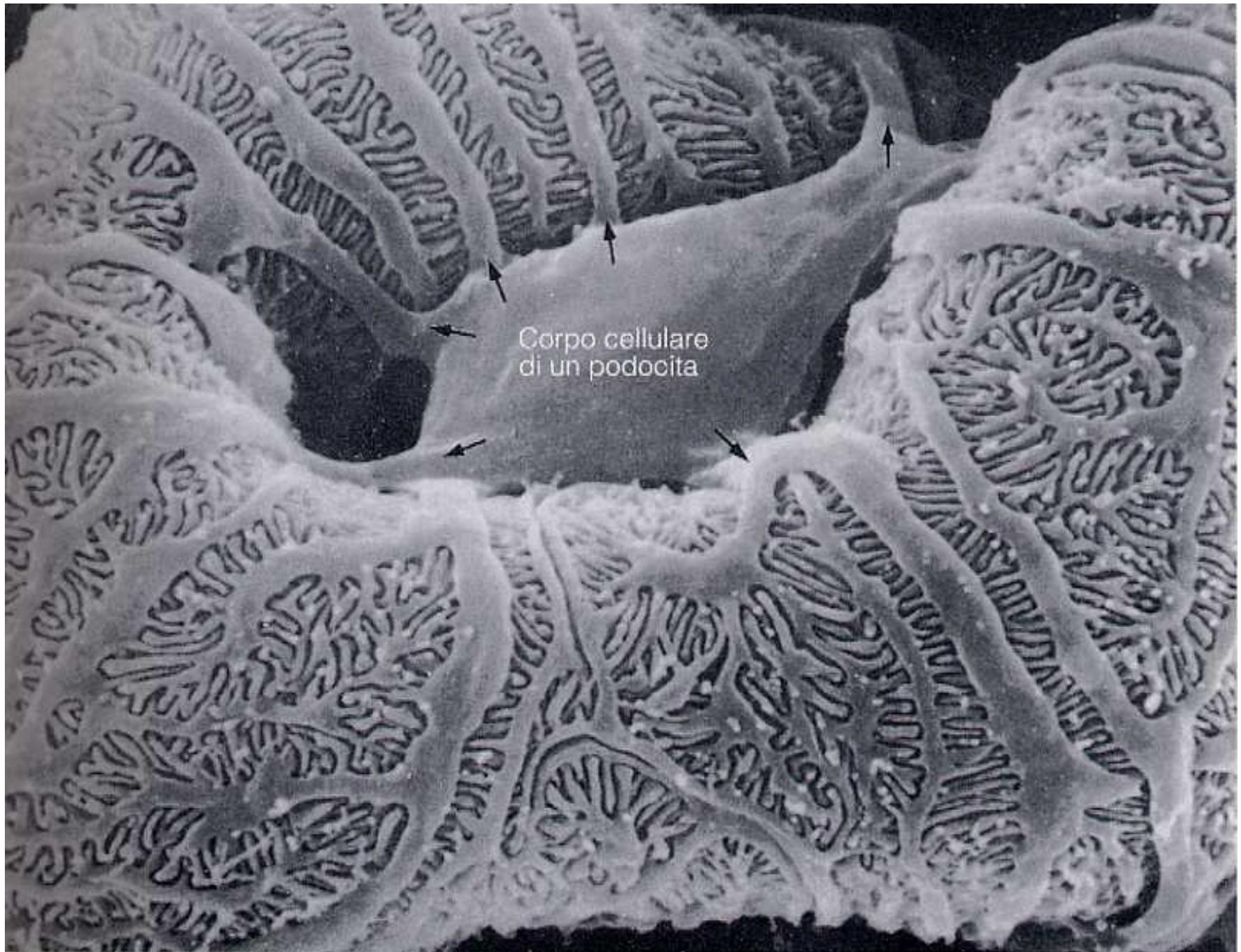
FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO
Sistema Sanitario Regione Lombardia



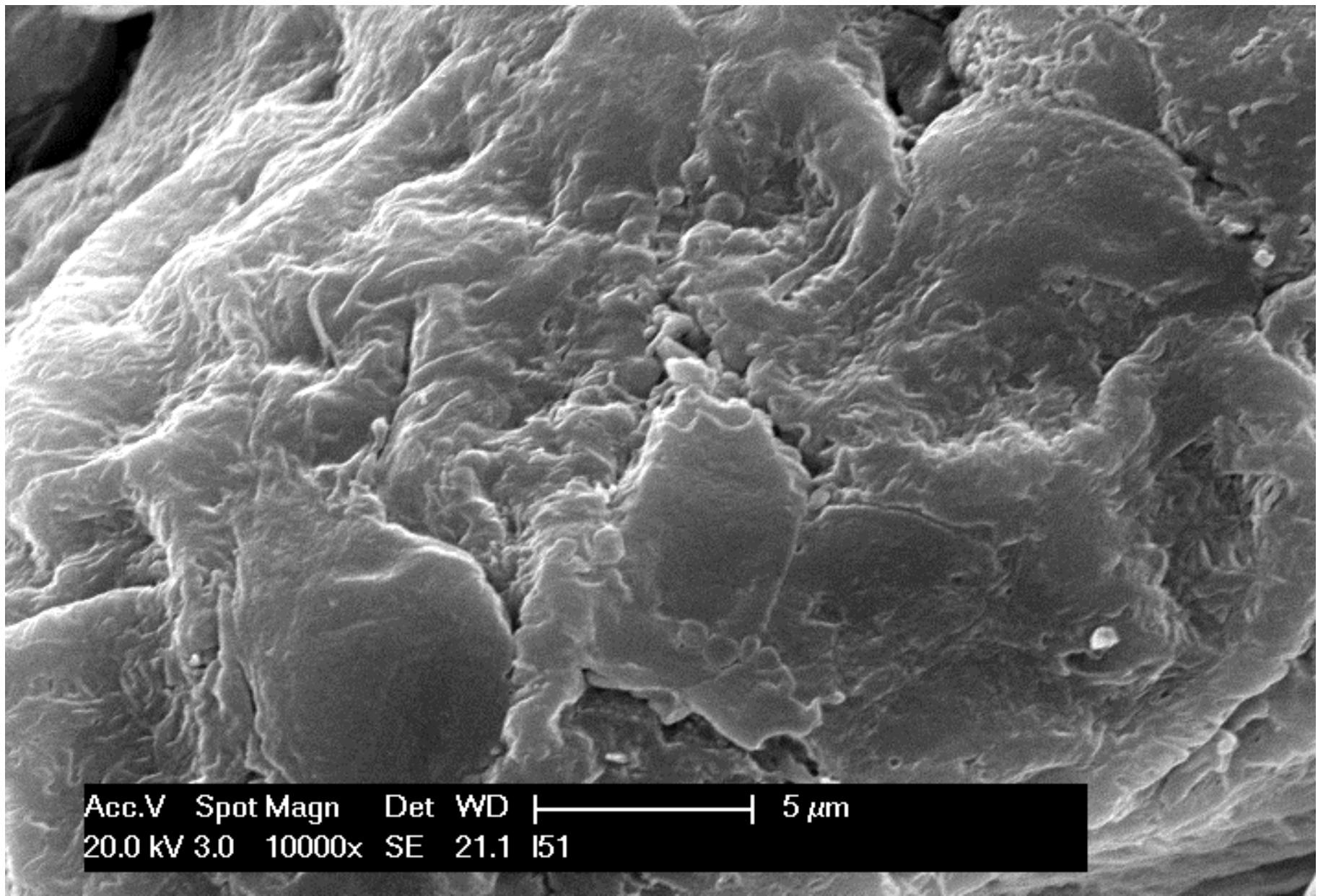
ASSOCIAZIONE PER IL
BAMBINO NEFROPATICO

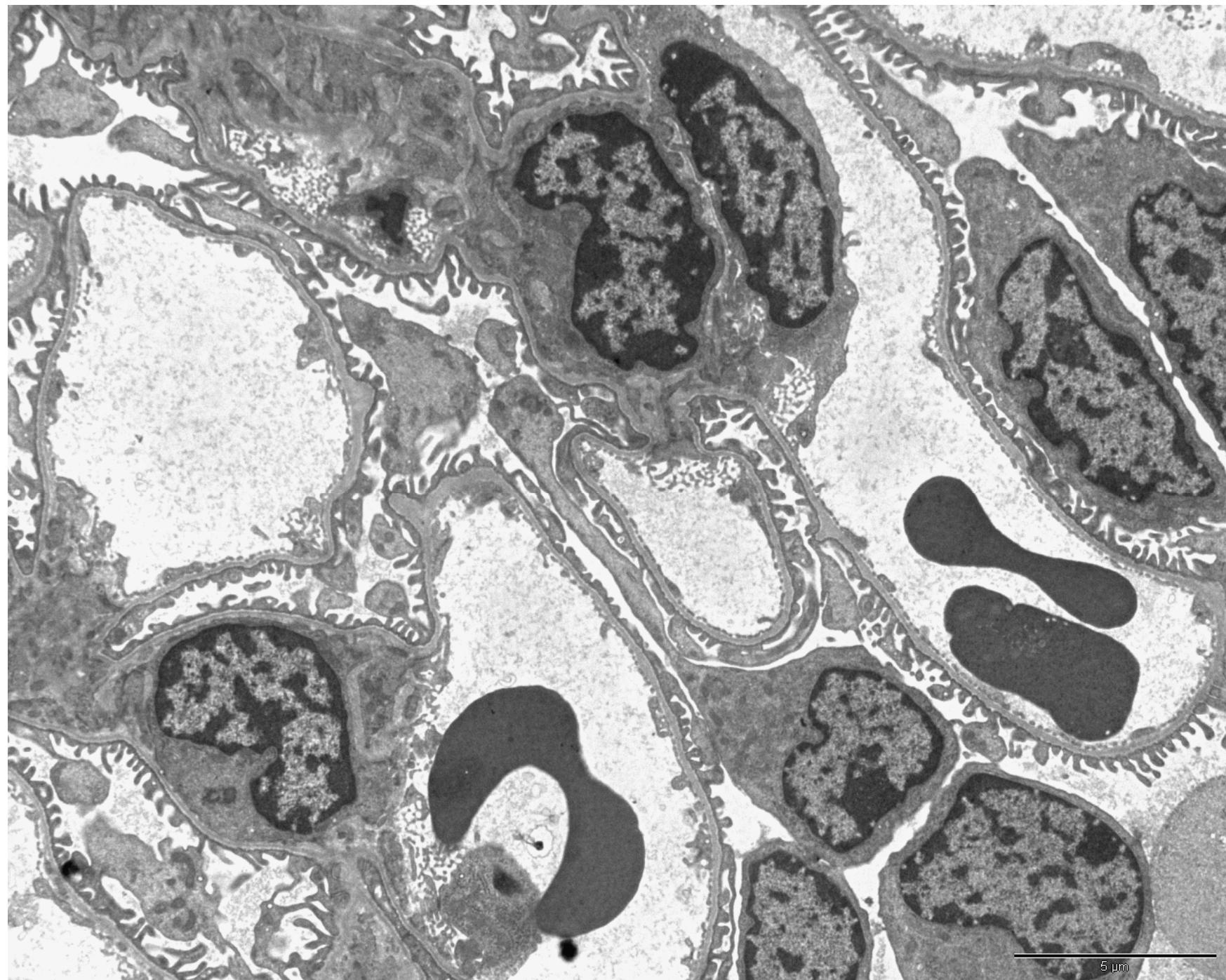


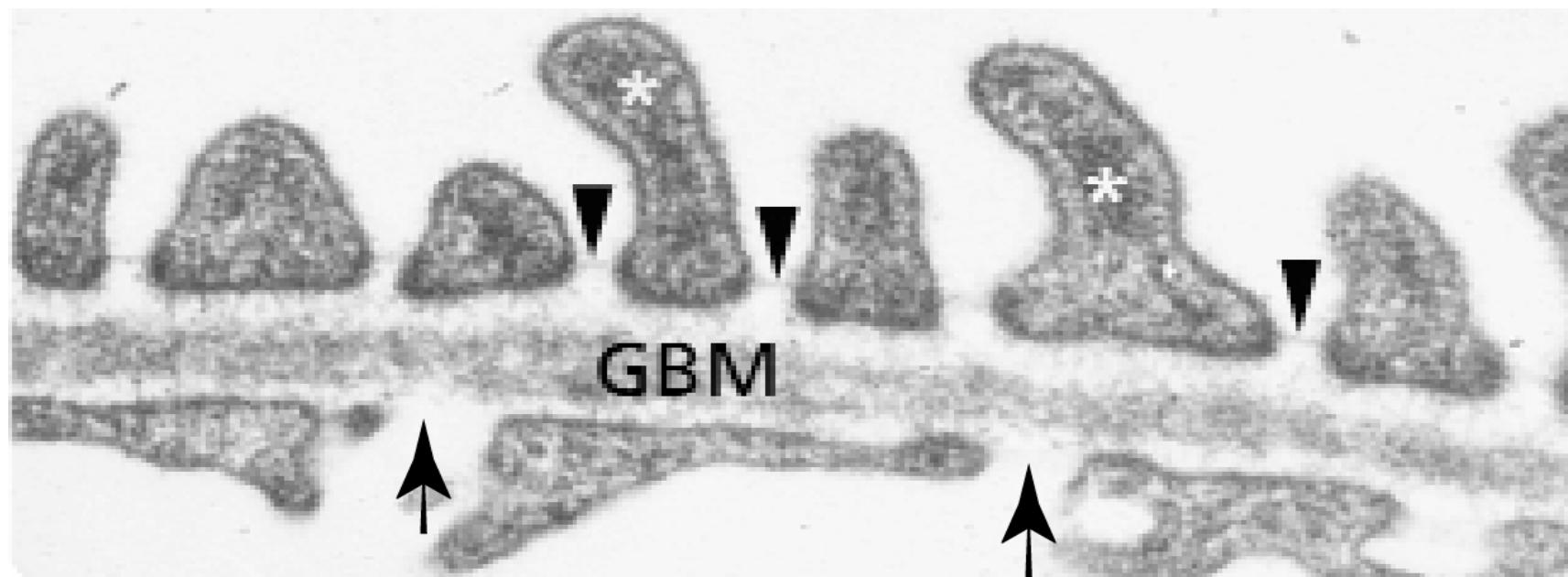




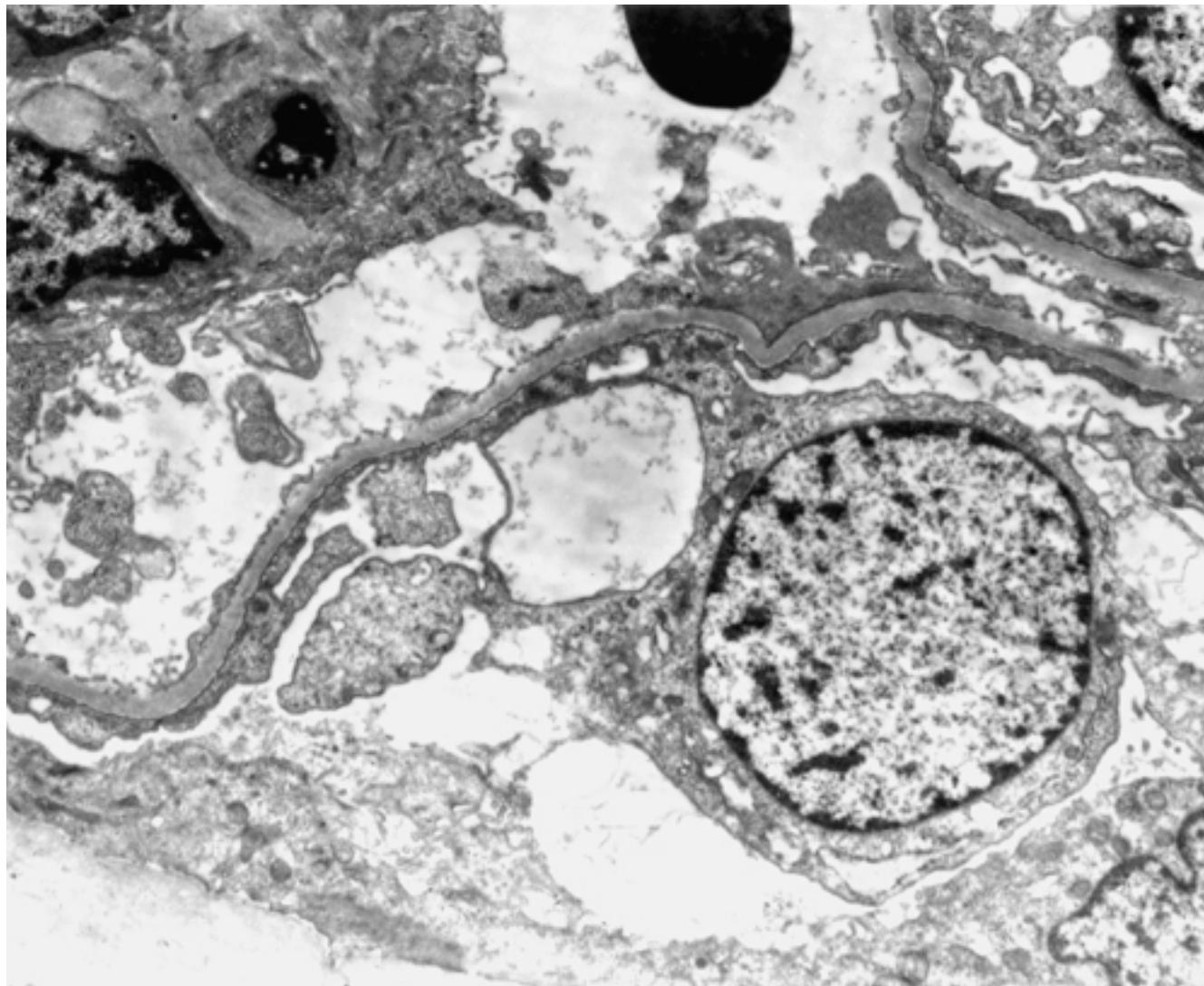
Corpo cellulare
di un podocita





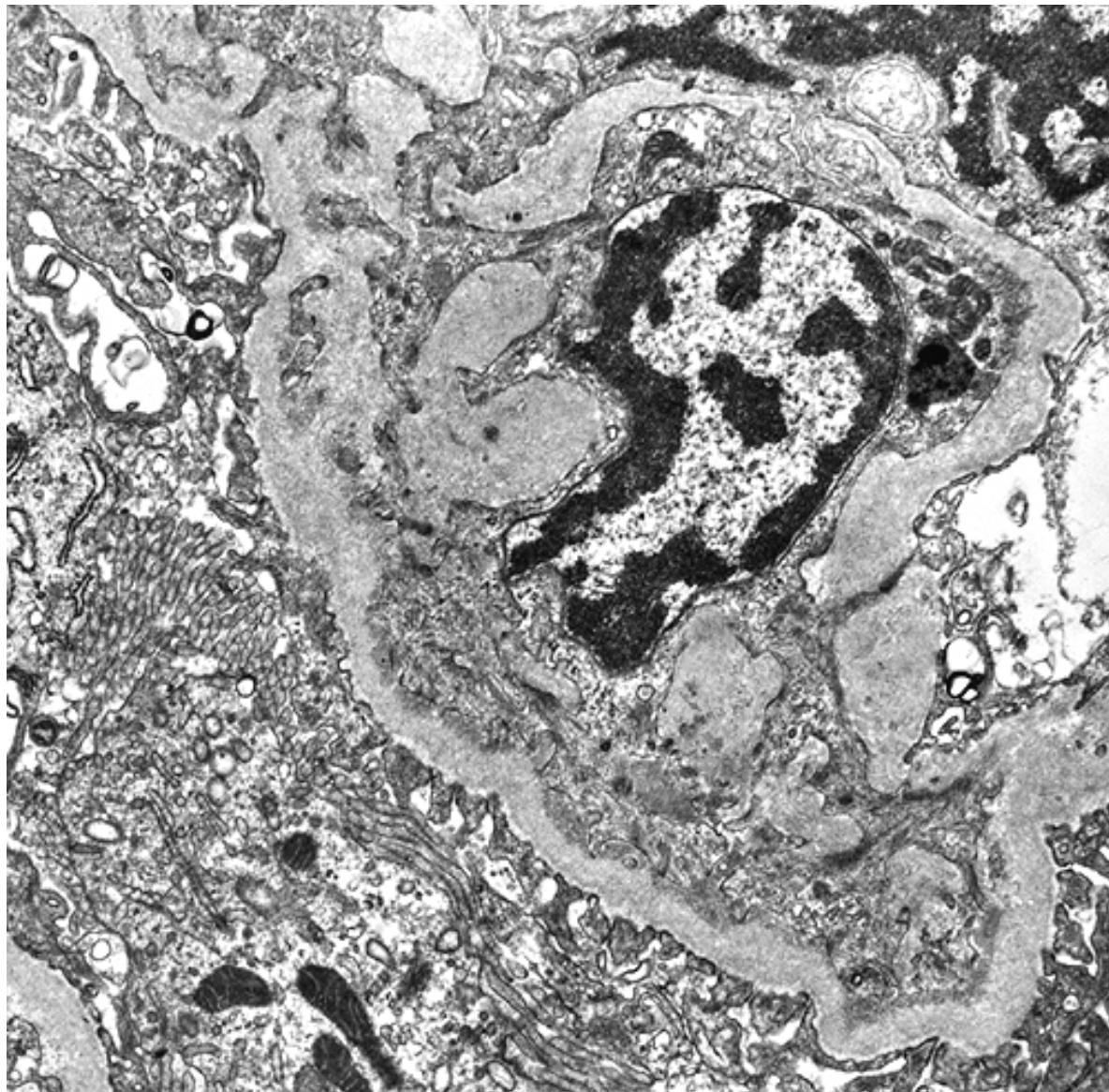


Minimal change disease



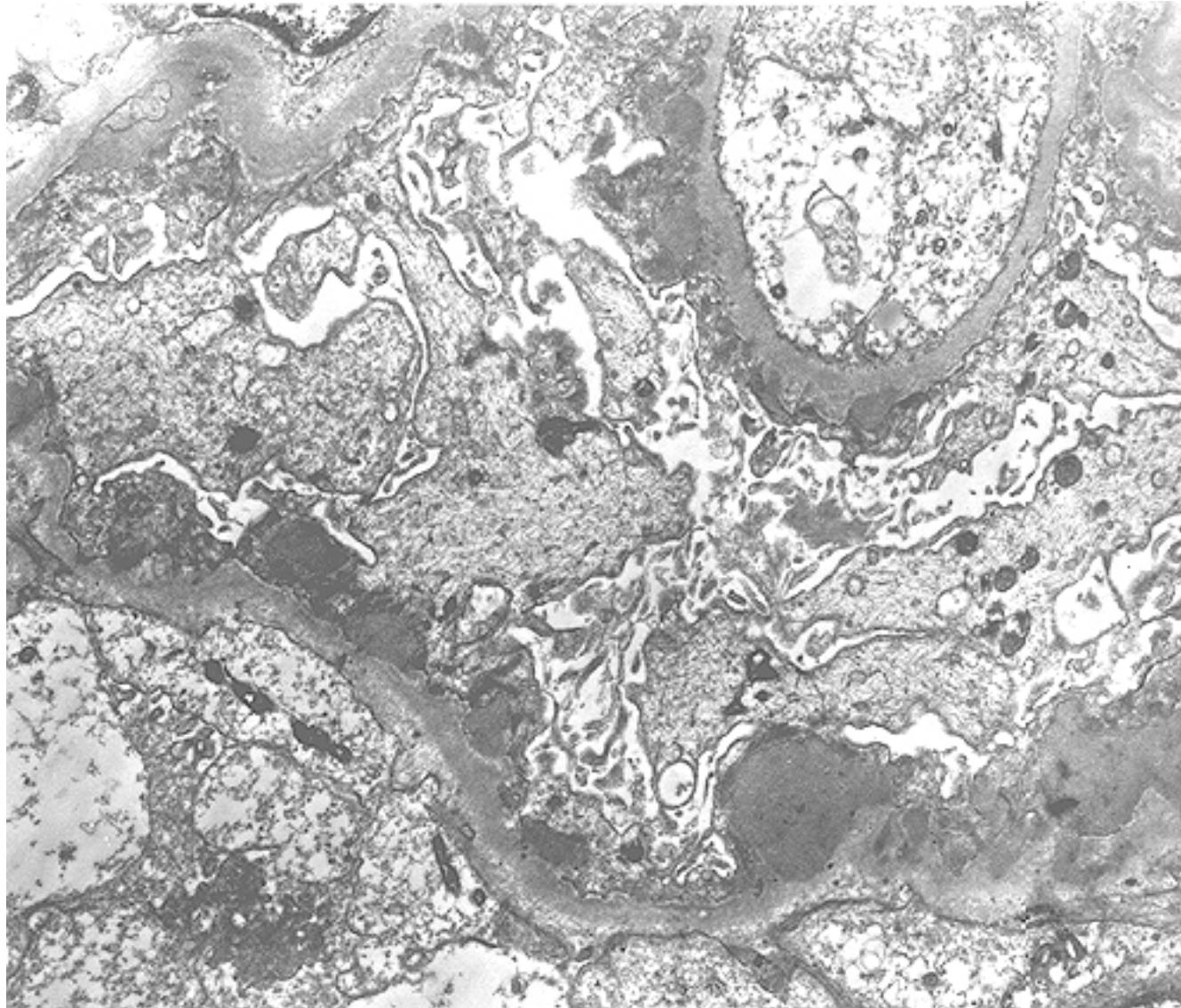
http://www.fondazionedamico.org/biopsiarenale_atlas/index.htm

Focal segmental glomerulosclerosis



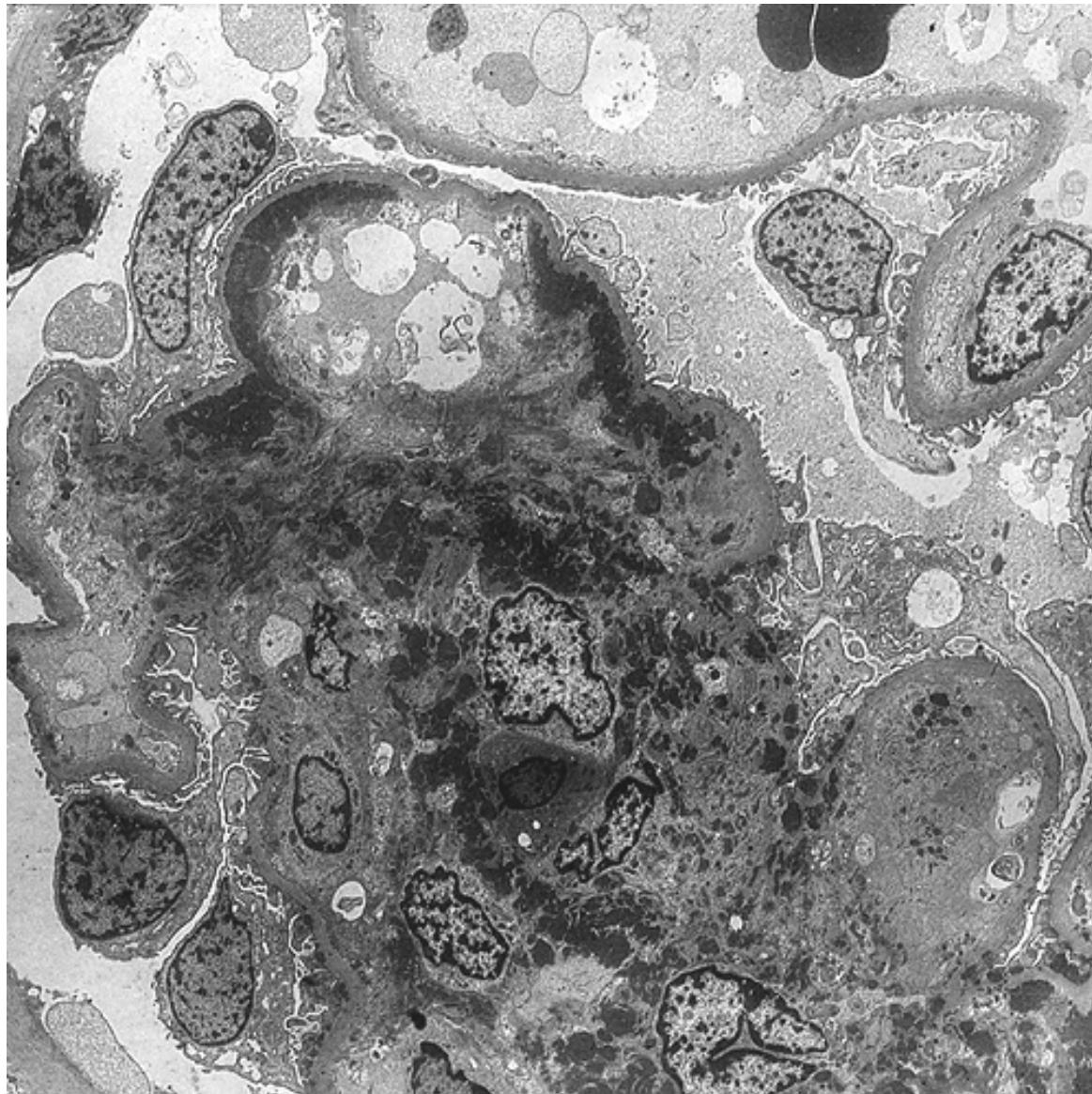
http://www.fondazionedamico.org/biopsiarenale_atlas/index.htm

Membranous nephropathy



http://www.fondazionedamico.org/biopsiarenale_atlas/index.htm

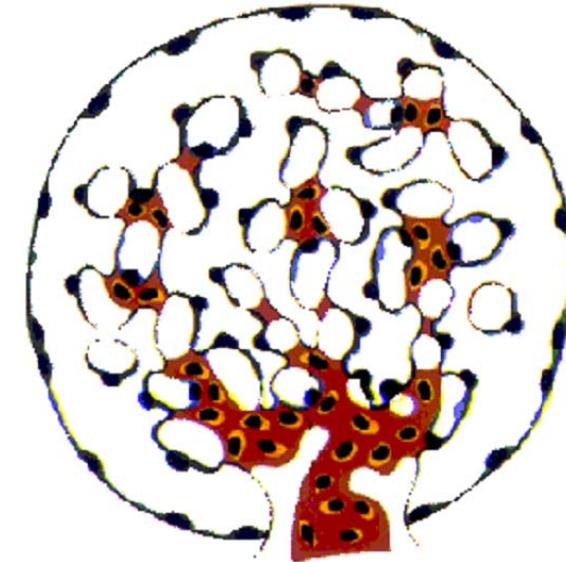
Lupus nephritis



http://www.fondazionedamico.org/biopsiarenale_atlas/index.htm

The kidneys together are receiving roughly 20% of cardiac output.

The entire blood volume passes through the renal filter every 5 min.

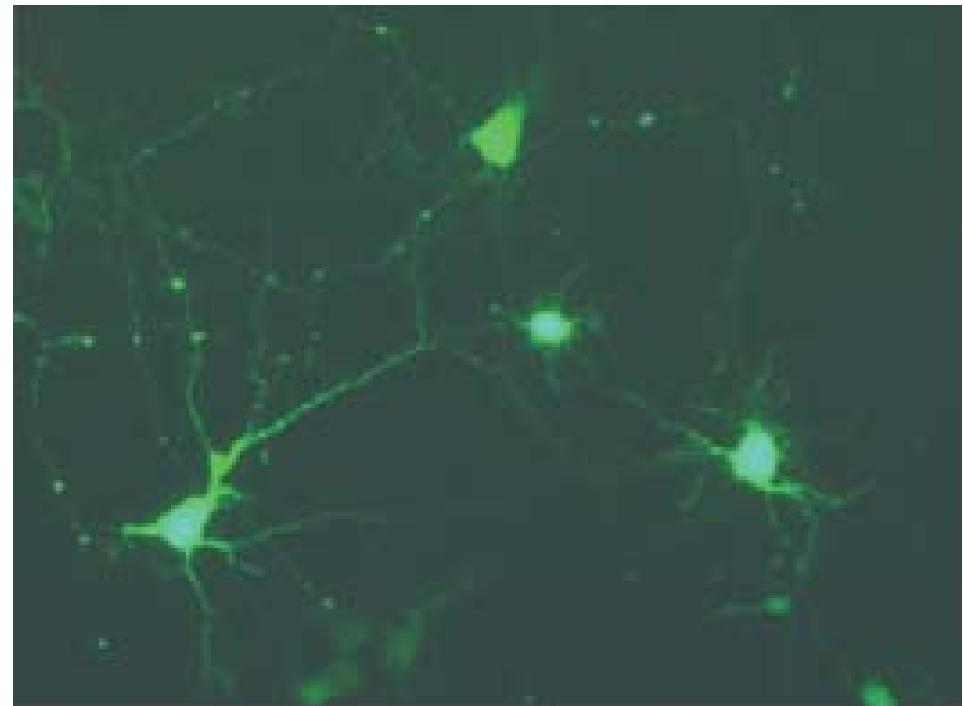
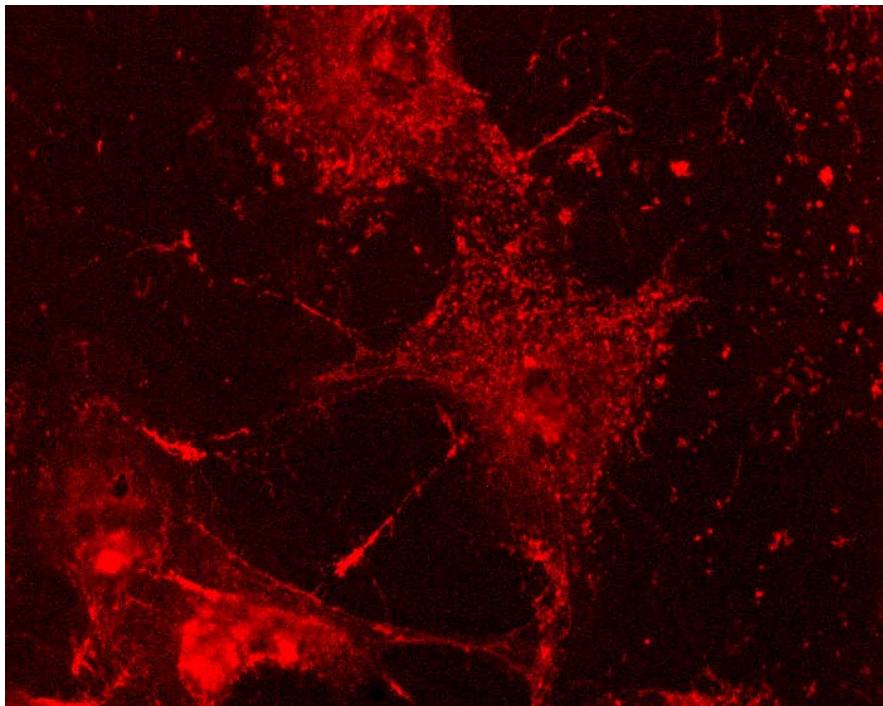


Therefore, glomerular cells are constantly exposed to an enormous variety of stimuli (blood pressure and content).

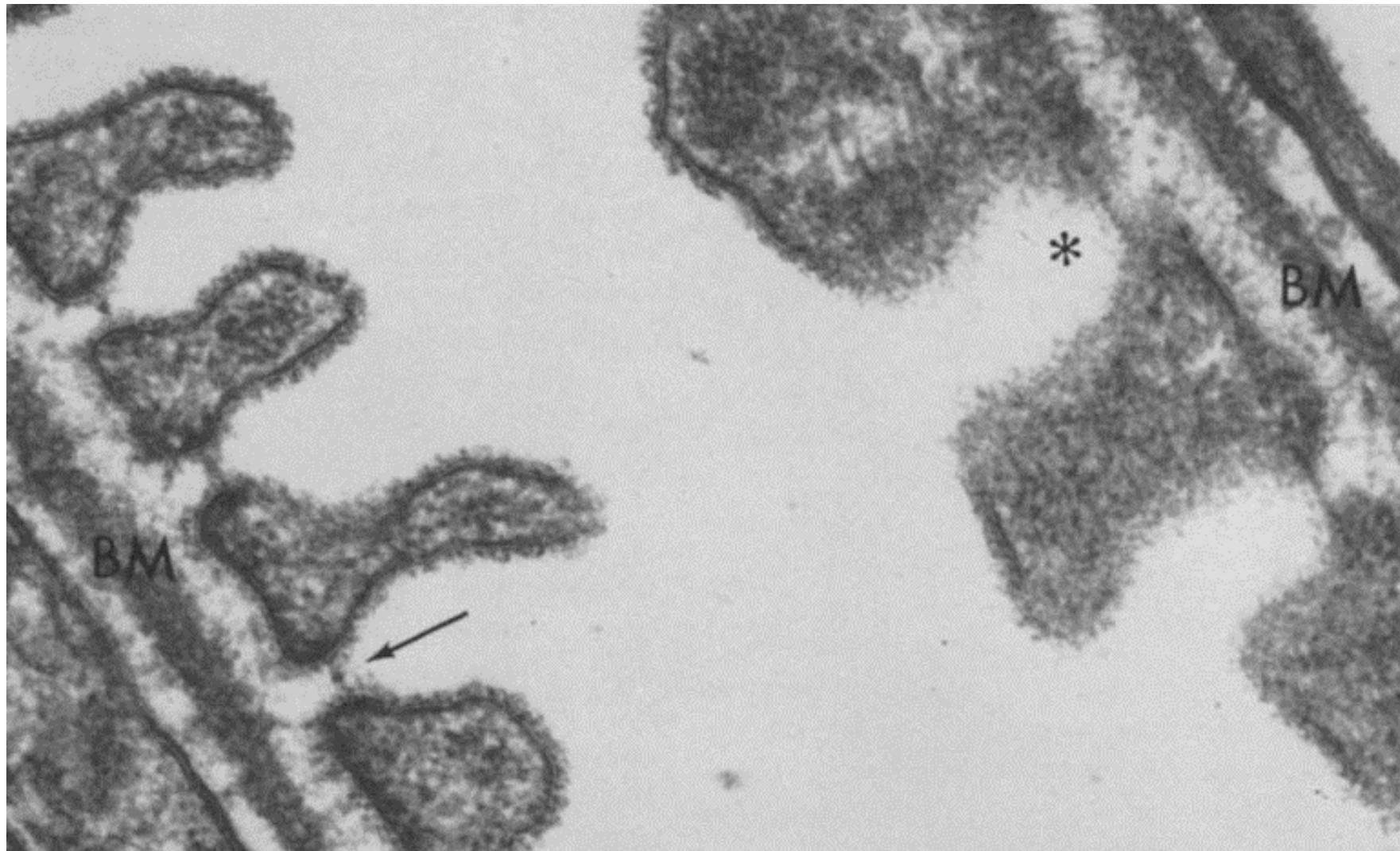
In this continuously varying environment, communication between glomerular cells becomes essential to the maintenance of a correct function of the glomerular filtration barrier.

Studies on this specific field are difficult because of the extremely convoluted structure of the renal glomerulus, but we can expect advances in the near future, given the enormous progresses in technologies that make it feasible the creation and subsequent analysis of animal models.

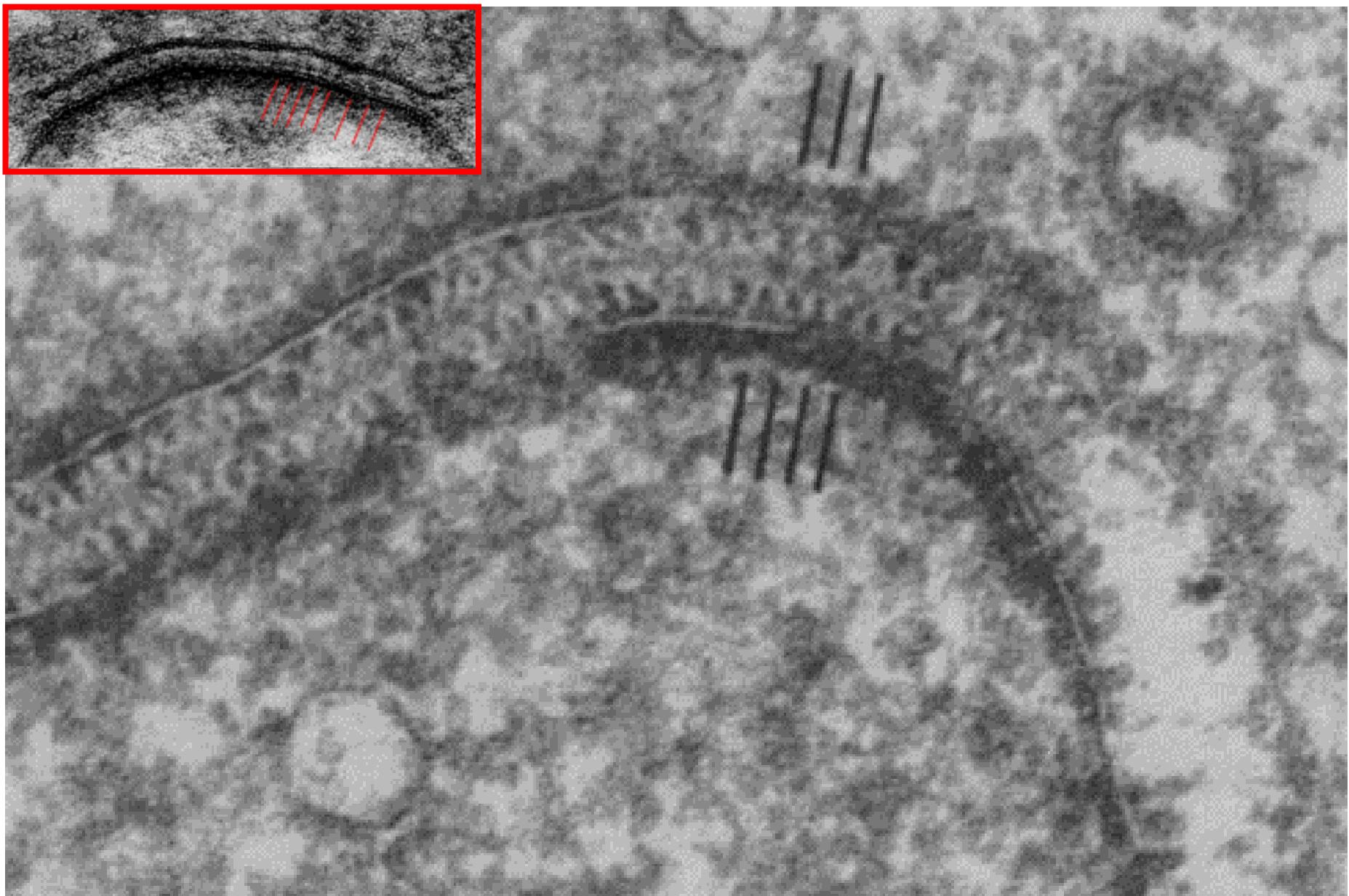
Synaptic-like communication: a morphologically-driven hypothesis



Highly ramified cells have a common cytoskeletal organization, use a common machinery of process formation, and have peculiar, specialised junctions, such as the slit diaphragm in podocytes and the synaptic junction in neuronal cells.



Rodewald R, Karnovsky MJ. J Cell Biol 60: 423-433, 1974



Rodewald R, Karnovsky MJ. J Cell Biol 60: 423-433, 1974

Type	Name	References		
		Podocytes	Neuronal cells	Astrocytes
Adhesion molecules	Nephrin	Ruotsalainen V, et al. Proc Natl Acad Sci U S A. 1999;96:7962-7.	Wanner N, et al. PLoS One. 2011;6:e23598.	-
	Neph1-3	Ristola M, et al. BMC Mol Biol. 2009;10:83.	Gerke P, et al. J Comp Neurol. 2006;498:466-75.	-
	Podocalyxin	Kerjaschki D, et al. J Cell Biol. 1984;98:1591-6.	Vitureira N, et al. PLoS One. 2010;5:e12003.	-
	EphrinB1	Hashimoto T, et al. Kidney Int. 2007;72:954-64.	Uchida H, et al. Neurochem Int. 2009;54:215-21.	Zhuang Z, et al. Commun Integr Biol. 2011;4:223-6.
	Neurexin-1	Saito A, et al. Am J Physiol Regul Integr Comp Physiol. 2011;300:R340-8.	Miller MT, et al. Structure. 2011;19:767-78.	Zhao H, et al. Synapse. 2011;65:433-40.
	Cadherins	Holthöfer H. Nephrol Dial Transplant. 2007;22:2124-8.	Brigidi GS, et al. Curr Opin Neurobiol. 2011;21:208-14.	Tran MD, et al. J Neurochem. 2008;105:272-86.
	Proto-cadherins	Ciani L, et al. Mol Cell Biol. 2003;23:3575-82.	Frank M, et al. Curr Opin Cell Biol. 2002;14:557-62.	Garrett AM, et al. J Neurosci. 2009;29:11723-31.
	Sidekick	Kaufman L, et al. J Biol Chem. 2010;285:25677-85.	Yamagata M, et al. Cell. 2002;110:649-60.	-
Receptors and channels	NMDAR	Anderson M, et al. Am J Physiol Cell Physiol. 2011;300:C22-32.	Bard L, et al. Mol Cell Neurosci. 2011;48:298-307.	Bardoni R, et al. J Physiol. 2010;588:831-46.
	Grm1	Puliti A, et al. Am J Pathol. 2011;178:1257-69.	Lüscher C, et al. Neuron. 2010;65:445-59.	Biber K, et al. J Neurochem. 1999;72:1671-80.

Type	Name	References		
Actin-binding	Synaptopodin	Podocytes Mundel P, et al. <i>J Cell Biol.</i> 1997;139:193-204.	Neuronal cells Deller T, et al. <i>J Comp Neurol.</i> 2000;418:164-81.	Astrocytes -
	Drebrin	Peitsch WK, et al. <i>J Am Soc Nephrol.</i> 2003;14:1452-63.	Dun XP, et al. <i>Mol Cell Neurosci.</i> 2012;49:341-50.	Butkevich E, et al. <i>Curr Biol.</i> 2004;14:650-8.
	Densin	Heikkilä E, et al. <i>Mol Cell Biochem.</i> 2007;305:9-18.	Carlisle HJ, et al. <i>J Neurosci.</i> 2011;31:16194-207.	-
	Adducin	Ferrandi M, et al. <i>J Mol Med (Berl).</i> 2010;88:203-17.	Stevens RJ, et al. <i>Curr Biol.</i> 2011;21:R402-5.	Shan X, et al. <i>Neuroscience.</i> 2005;134:833-46.
	Alpha-actinin4	Cybulsky AV, et al. <i>J Signal Transduct.</i> 2011;2011:563128.	Schnizler MK, et al. <i>J Biol Chem.</i> 2009;284:2697-705.	Jeffcoat S, et al. <i>Cytobios.</i> 1995;82:81-99.
Other	Dendrin	Patrakka J, et al. <i>J Am Soc Nephrol.</i> 2007;18:689-97.	Herb A, et al. <i>Mol Cell Neurosci.</i> 1997;8:367-74.	-
	Fyn	Verma R, et al. <i>J Biol Chem.</i> 2003;278:20716-23.	Babus LW, et al. <i>Brain Res.</i> 2011;1415:96-102.	Chun JT, et al. <i>Exp Neurol.</i> 2004;185:109-19.
	PTPRO (Glepp1)	Thomas PE, et al. <i>J Biol Chem.</i> 1994;269:19953-62.	Beltran PJ, et al. <i>J Comp Neurol.</i> 2003;456:384-95.	-

Top biological processes - ToppGene analysis

vesicle mediated transport: 72 genes

actin cytoskeleton organization: 39 genes

regulation of signaling: 99 genes

neurogenesis (74 genes), neuron projection development (52 genes), axon guidance (33 genes)

biological adhesion: 59 genes

response to oxygen levels: 19 genes

neuromuscular junction: 7 genes

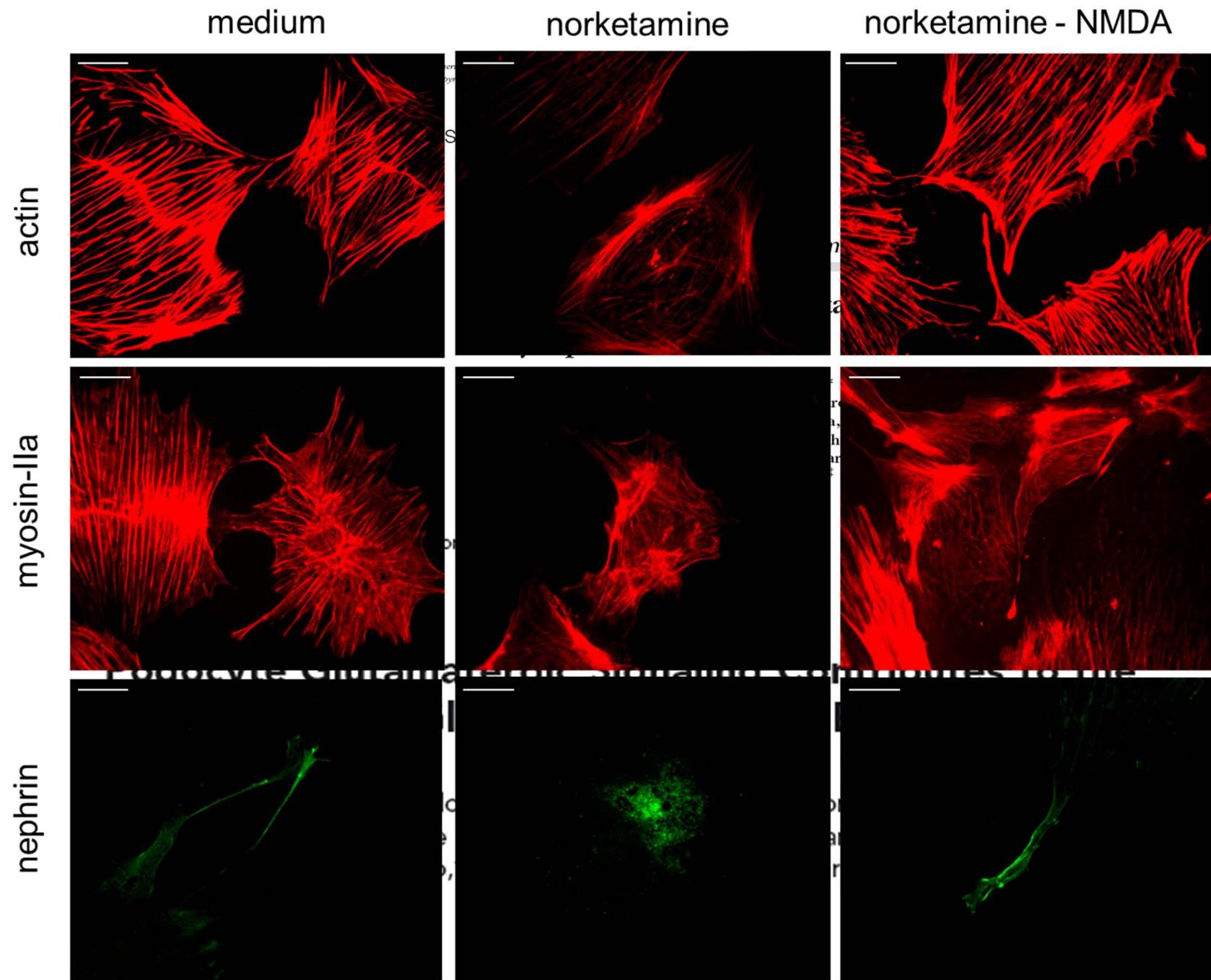
chemotaxis: 38 genes

phagocytosis: 11 genes

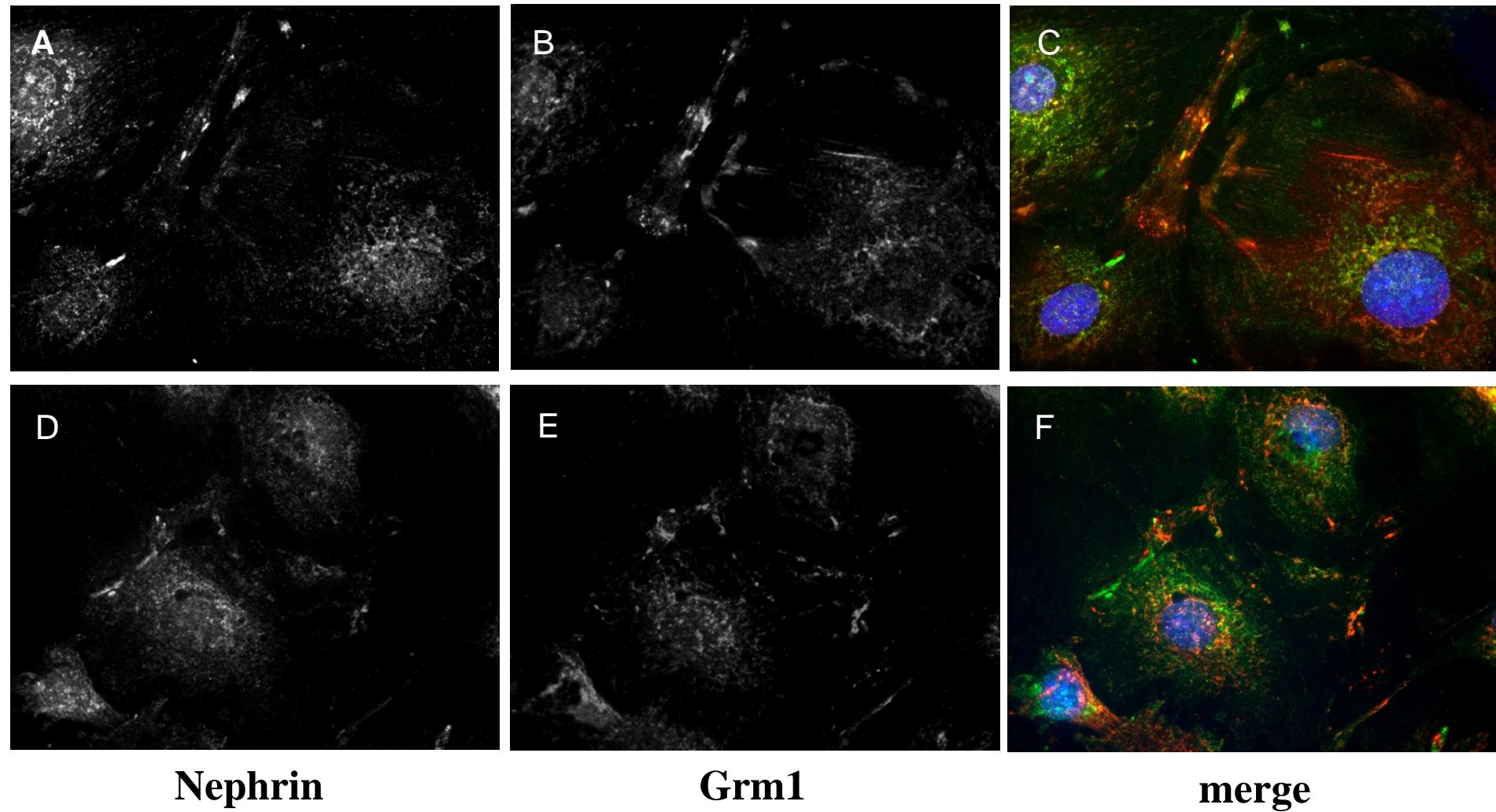
striated muscle cell differentiation: 16 genes

muscle contraction: 20 genes

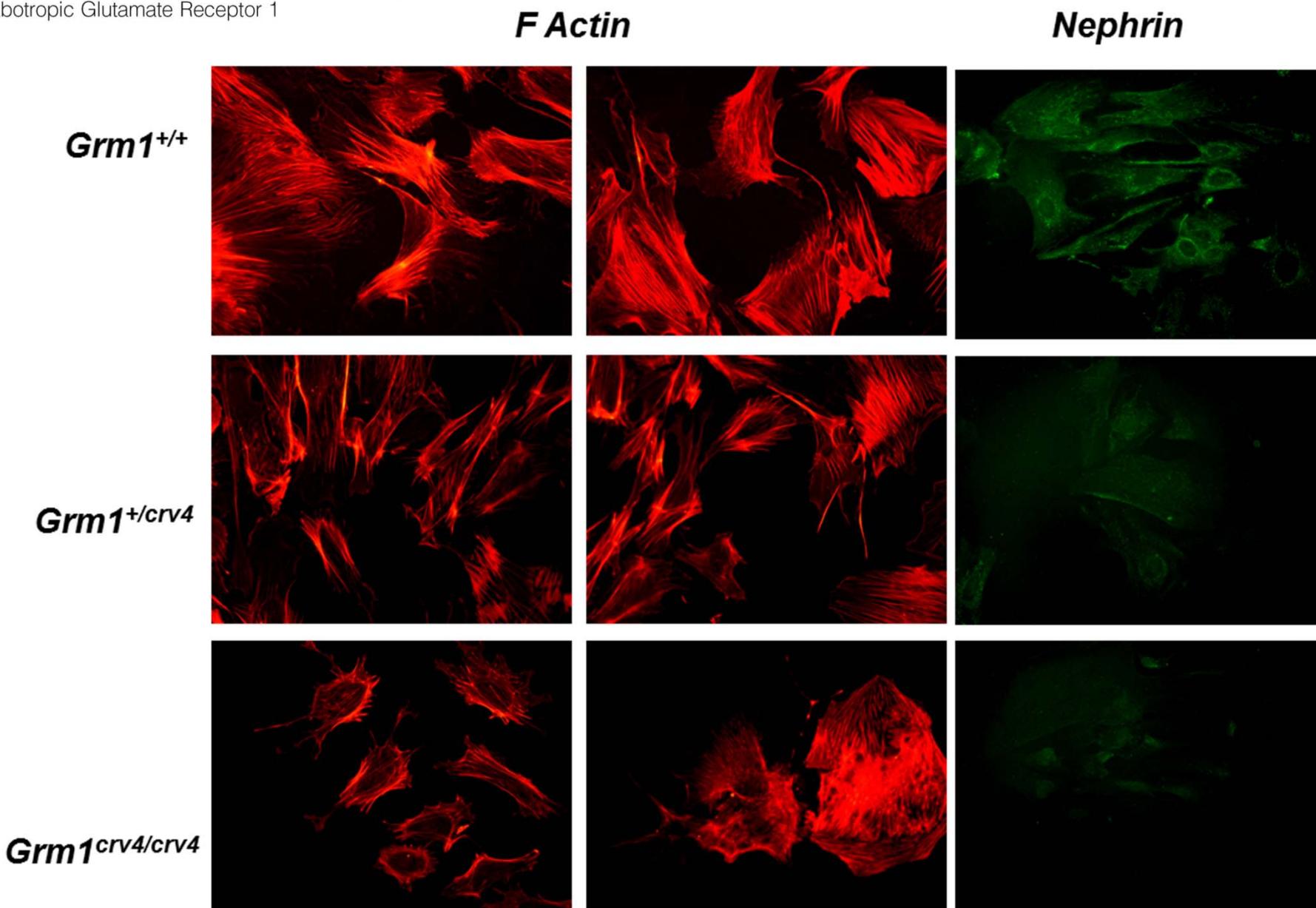
**“The biological process analysis
shows a strong neuronal character”**

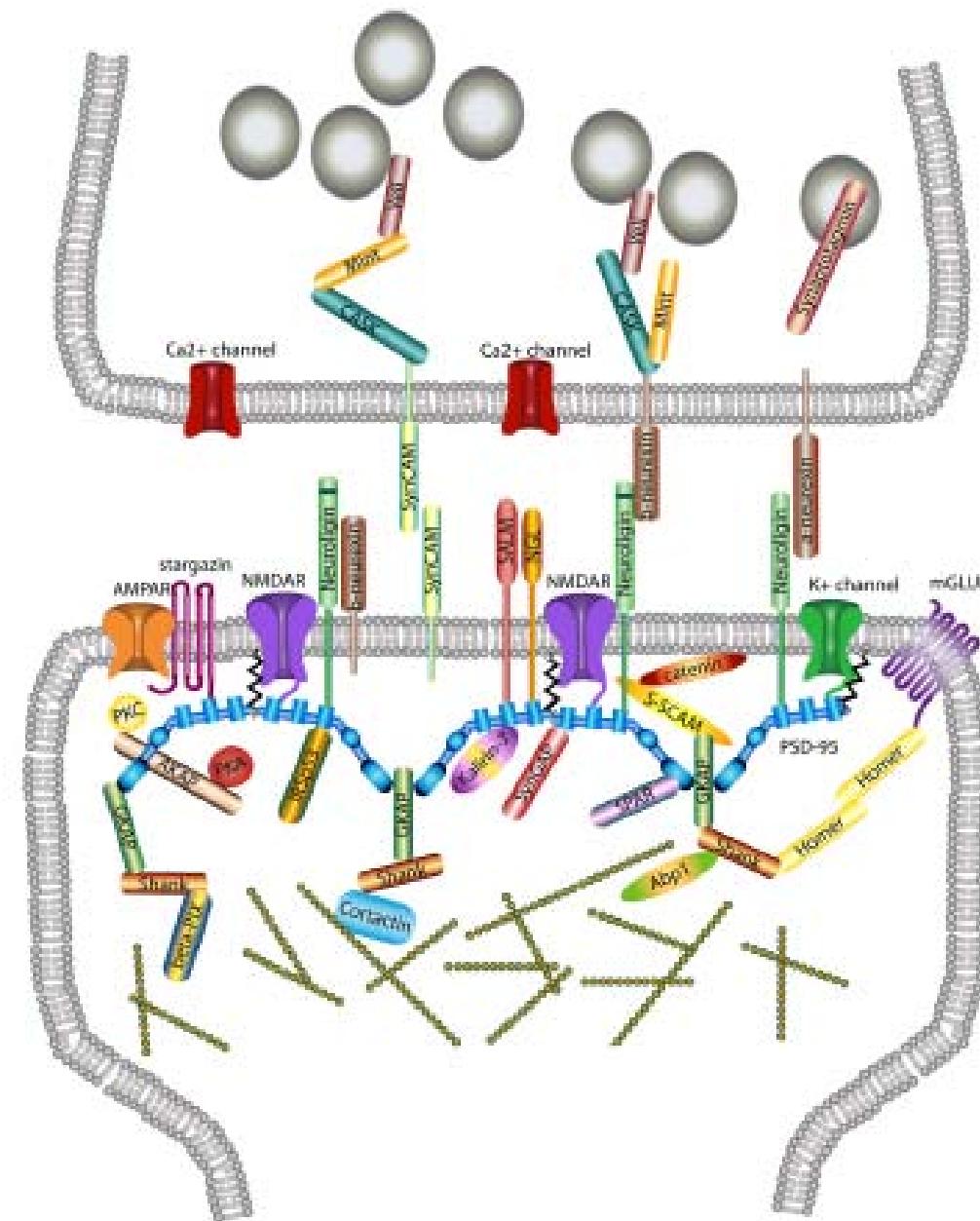


Albuminuria and Glomerular Damage in Mice Lacking the Metabotropic Glutamate Receptor 1



Albuminuria and Glomerular Damage in Mice Lacking the Metabotropic Glutamate Receptor 1





At synapses, Ig-like adhesion molecules, among other synaptic adhesion molecules (such as cadherins, ephrins and ephrin receptors) recruit synaptic vesicles, cluster neurotransmitter receptors, and link neurotransmitter receptors to scaffolding molecules, such as PSD95, to convey signals to the actin cytoskeleton.

Nephrin expression in adult rodent central nervous system and its interaction with glutamate receptors

Min Li,¹ Silvia Armelloni,¹ Masami Ikehata,¹ Alessandro Corbelli,^{1,2} Marzia Pesaresi,^{1,3} Novella Calvaresi,¹ Laura Giardino,¹ Deborah Mattinzoli,¹ Francesca Nisticò,¹ Serena Andreoni,¹ Aldamaria Puliti,^{4,5} Roberto Ravazzolo,^{4,5} Gianluigi Forloni,³ Piergiorgio Messa¹ and Maria Pia Rastaldi^{1*}

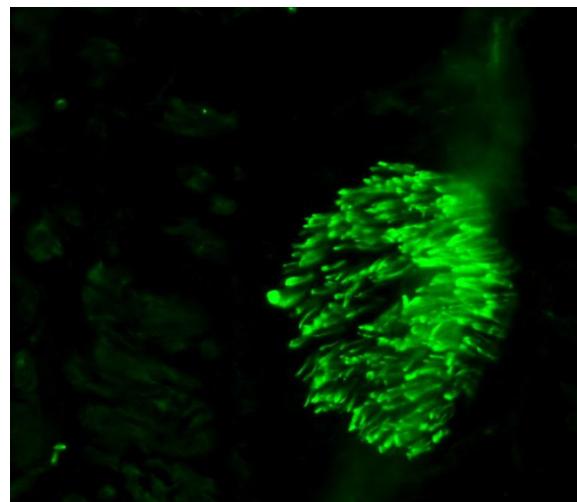
¹ Renal Research Laboratory, Department of Nephrology, Dialysis and Renal Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and Fondazione D'Amico per la Ricerca sulle Malattie Renali, Milan, Italy

² MIA Consortium, Università Milano Bicocca, Monza, Italy

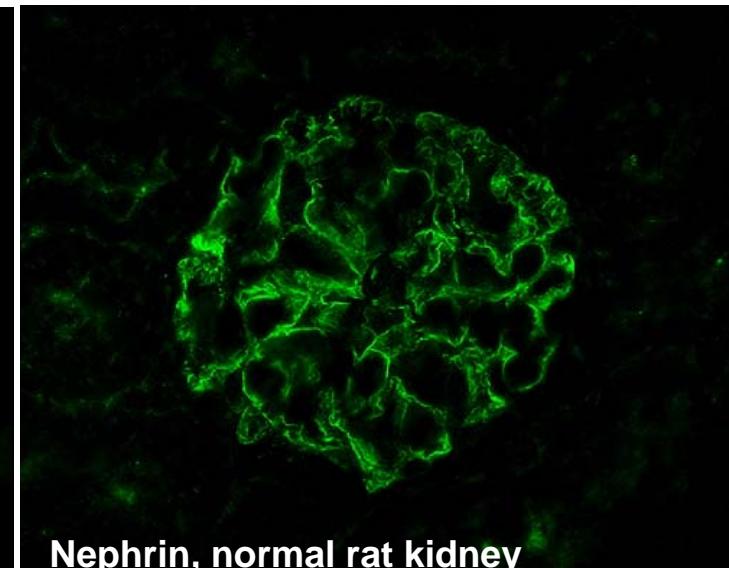
³ Department of Neuroscience, Mario Negri Institute, Milan, Italy

⁴ Department of Paediatric Sciences, University of Genova, Italy

⁵ Molecular Genetics and Cytogenetics Unit, Gaslini Institute, Genova, Italy

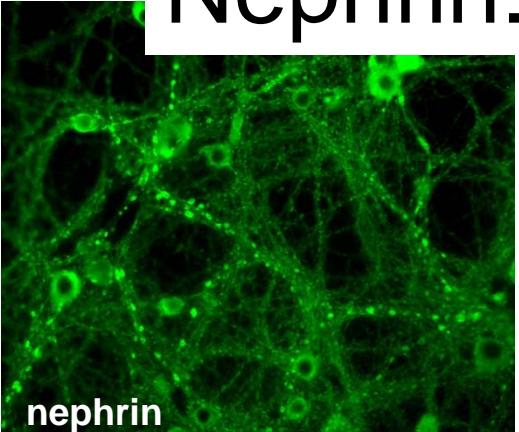


Nephrin, normal rat kidney

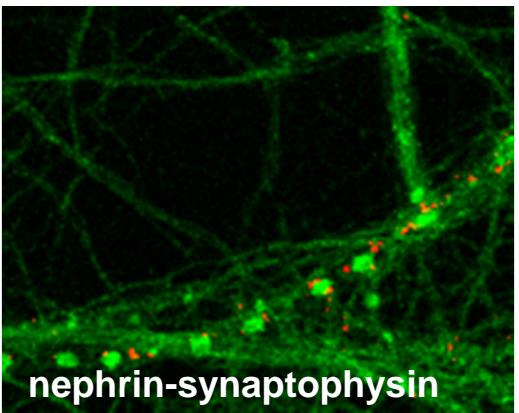


Nephrin, normal rat kidney

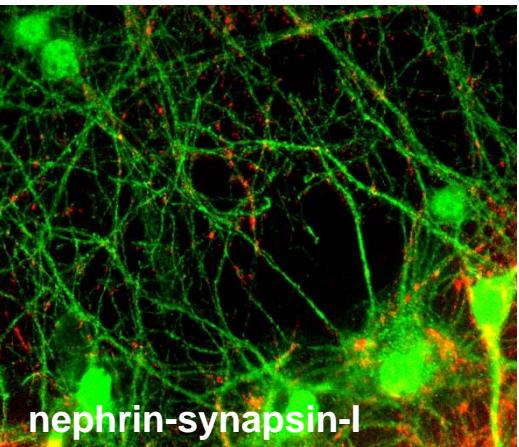
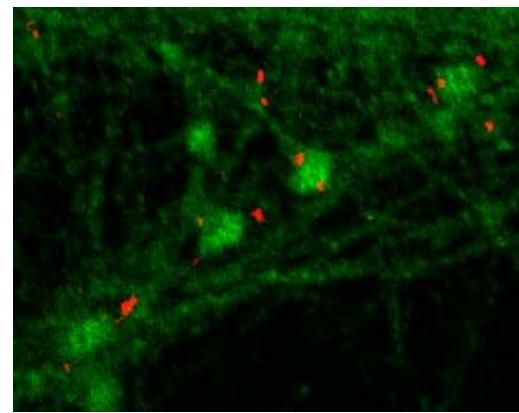
Nephrin: neurons and podocytes



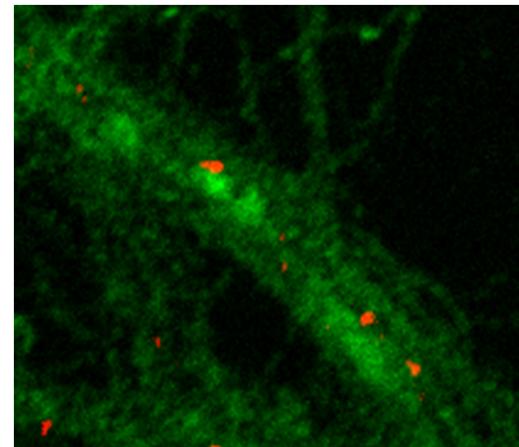
Primary
neuronal cells



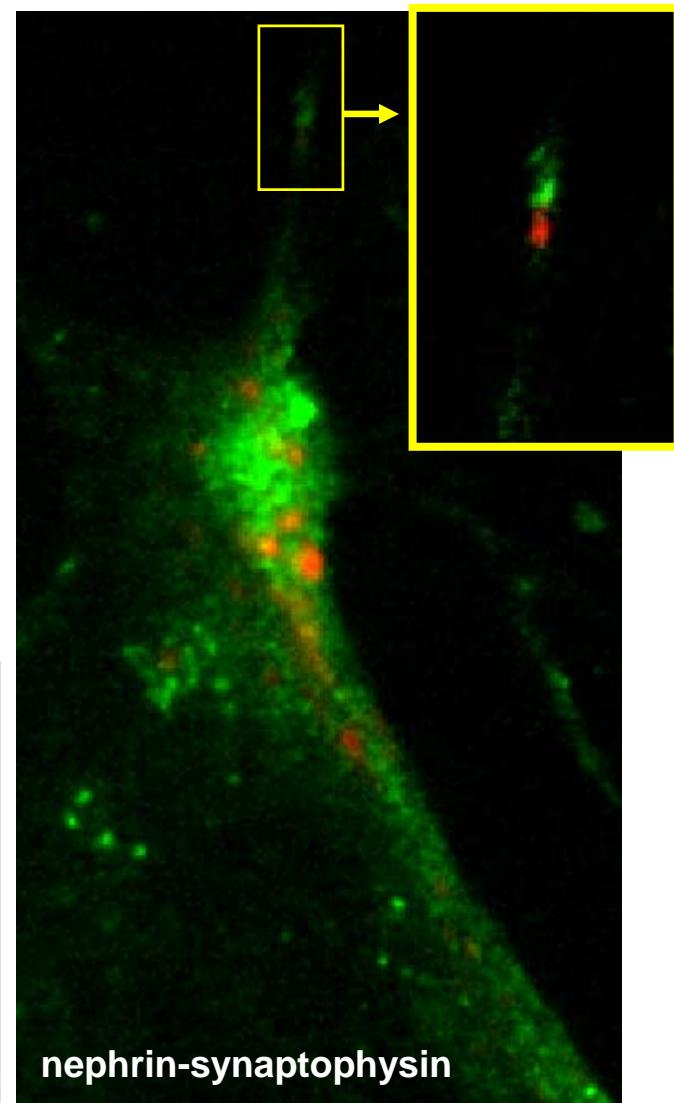
nephrin-synaptophysin



nephrin-synapsin-I



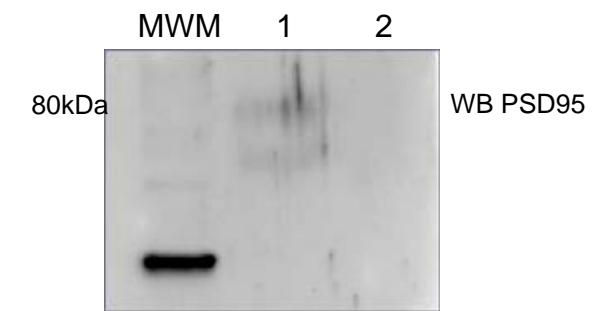
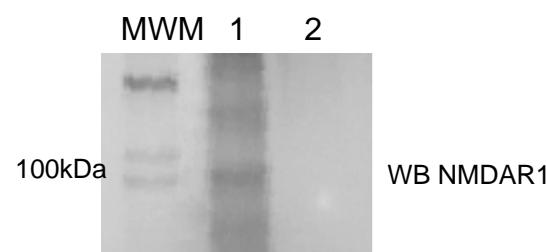
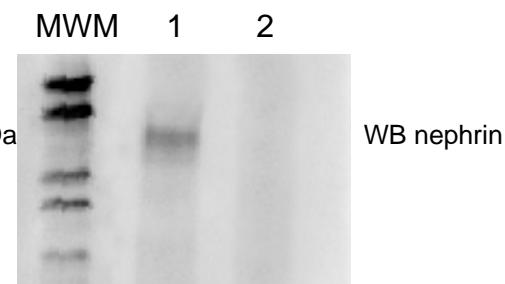
Primary podocytes



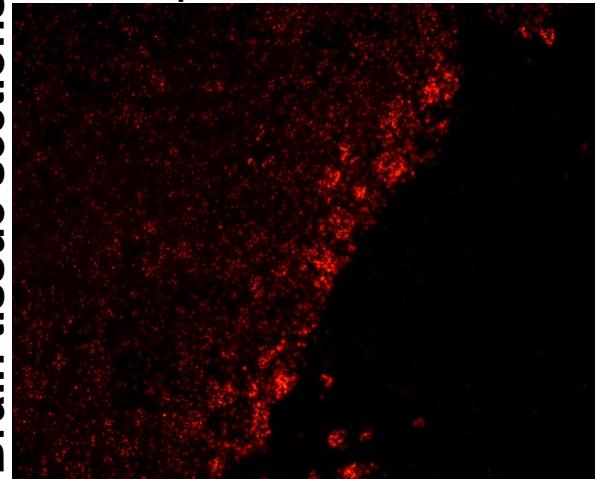
nephrin-synaptophysin

Nephrin – rodent CNS

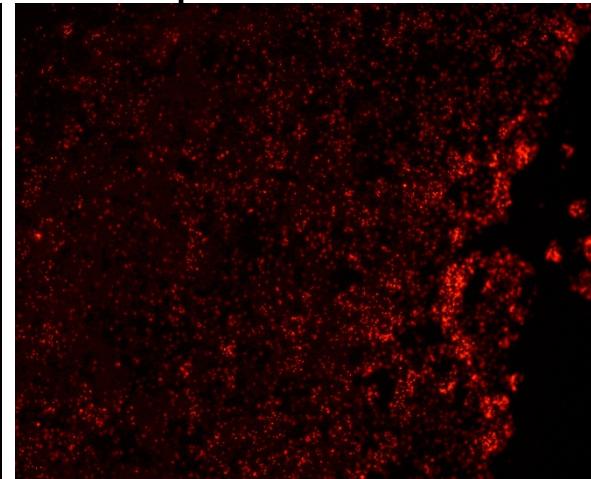
Brain – IP nephrin



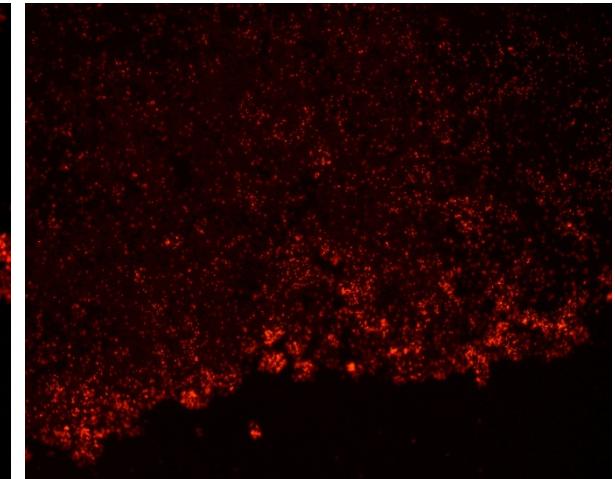
Nephrin-NMDAR



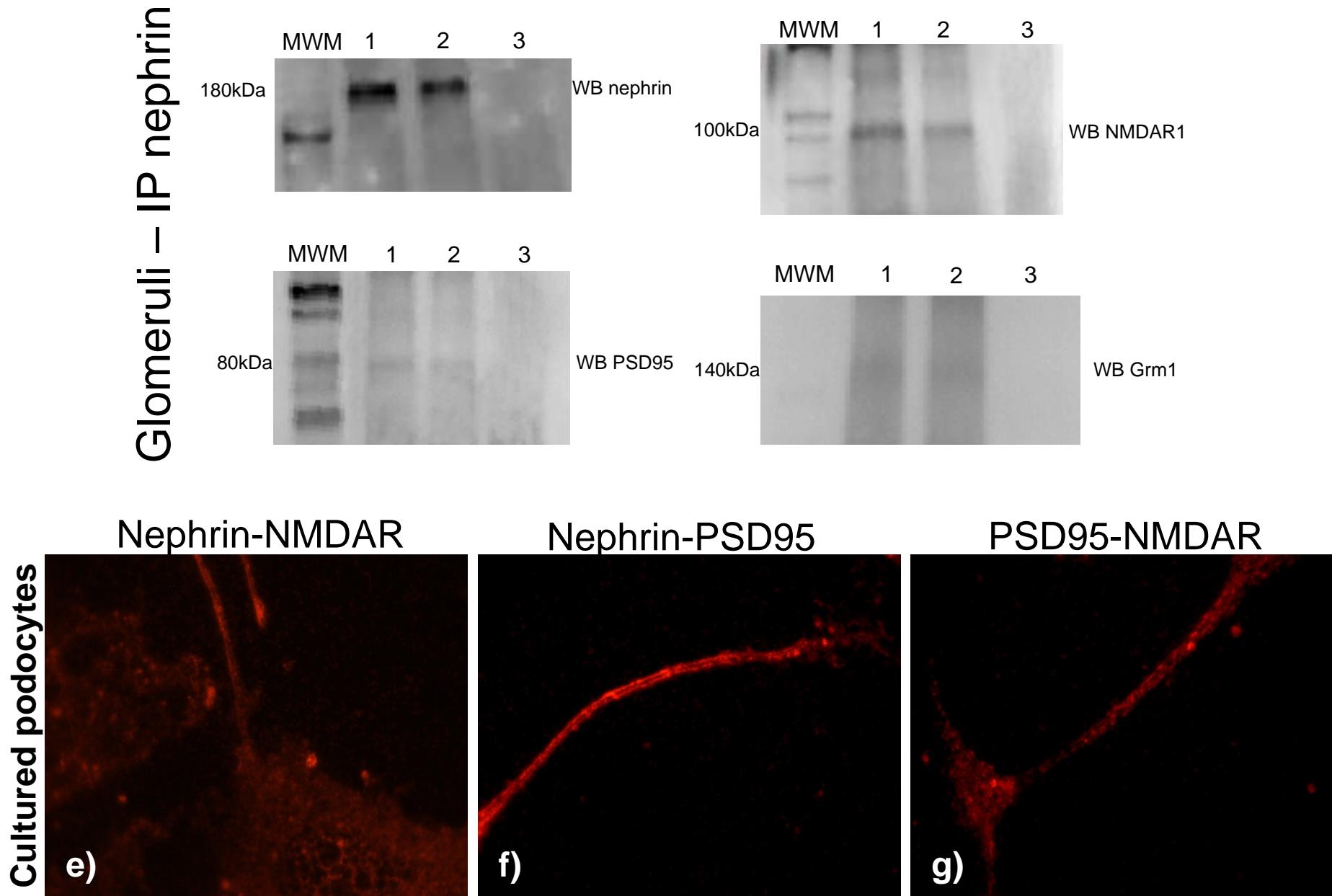
Nephrin-PSD95

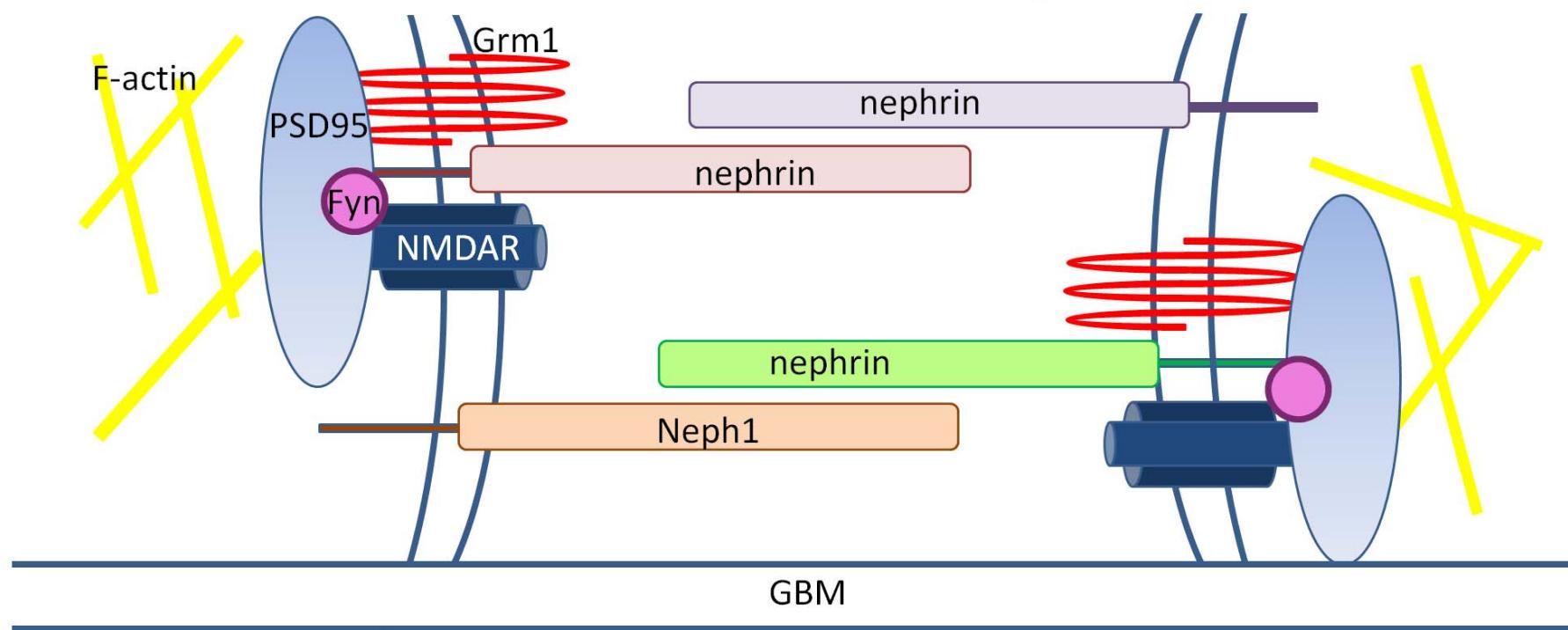
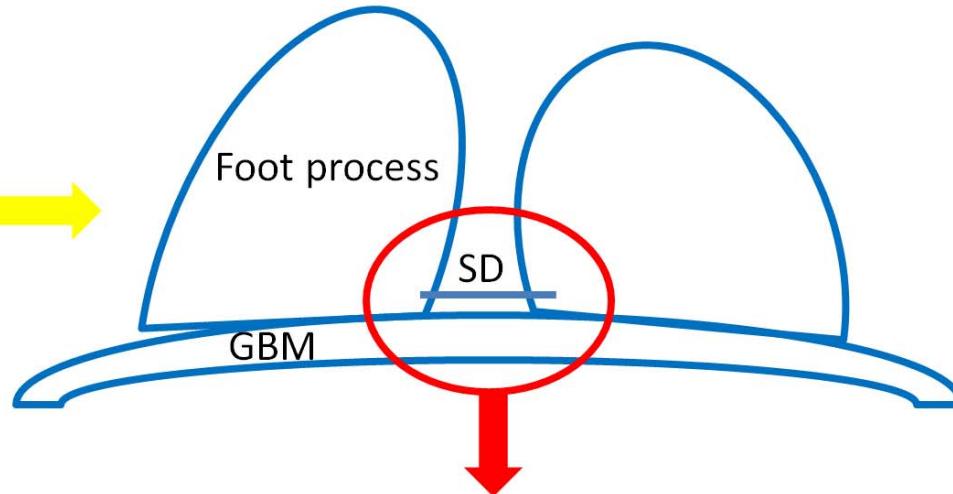
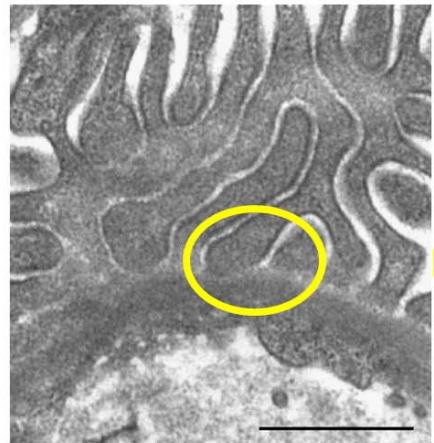


PSD95-NMDAR



Nephrin – glomeruli and podocytes





Conclusions

Podocytes use a neuron-like system of signalling, which is important to maintain proper filter capabilities. Variability among cells and presence of spontaneous signalling are opening fascinating research perspectives.

We are starting to better understand the molecular and functional properties of this type of communication, that can potentially be targeted by a series of already existing drugs.

The molecules involved are altered in human nephrotic syndrome, and their expression changes, which need to be more systematically analyzed, can be relevant to guide therapy.

Acknowledgments

Renal Research Laboratory, Milan

S. Armelloni: cell biology, transfection experiments
M. Li: 3D co-culture model, animal models
A. Corbelli: electron microscopy, immunogold EM
L. Giardino: in vivo microscopy
M. Ikehata: immunohistochemistry
A. Mondini: neurophysiology experiments
D. Mattinzoli: FACS analysis

Gaslini Institute, University of Genoa

A. Puliti, G. Caridi, R. Ravazzolo: Grm1-KO model

Trieste University

C. Zennaro: PAlb test, atomic force microscopy, Zebrafish studies

School of Biosciences, Cardiff University, Cardiff UK

PJ Kemp, D. Riccardi: neurophysiology